UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/981,020	10/16/2001	Daniel S. Kohane	0492611-0417 (MIT 8966)	5504

24280 7590 06/12/2008

CHOATE, HALL & STEWART LLP
TWO INTERNATIONAL PLACE
BOSTON, MA 02110

EXAMINER	
FUBARA, BLESSING M	

ART UNIT	PAPER NUMBER
1618	

NOTIFICATION DATE	DELIVERY MODE
06/12/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@choate.com

Office Action Summary	Application No.	Applicant(s)	
	09/981,020	KOHANE ET AL.	
	Examiner	Art Unit	
	BLESSING M. FUBARA	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *07 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7-15,17-20,23-25,27,30,37,47,58-65,80,84,86-91 and 96-107* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7-15,17-20,23-25,27,30,37,47,58-65,80,84,86-91 and 96-107* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner acknowledges receipt of request for extension of time, amendment and remarks filed 03/07/08. Claims 16, 21, 22, 26, 28, 29, 31-36, 38-46 and 85 are canceled. New claims 99-107 are added. Claims 1, 7-15, 17, 62-65, 86-91 and 96-98 are amended. Thus claims 1,7-15,17-20,23-25,27,30,37,47,58-65,80,84,86-91 and 96-107 are pending.

Previous rejections that are not reiterated herein are withdrawn.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1,7-15,17-20,23-25,27,30,37,47,58-65,80,84,86-91 and 96-107 remain/are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is new matter rejection.

The original specification does not envision microparticle composition that is not a liposome or does not comprise synthetic polymer. Applicant, for example, studied biocompatibility of

particles in terms of inflammatory response and gross neural injury and mentions Yanez et al. and "touch evoked agitation" as it relates to injections of liposomes (paragraphs [0139] and [0152] of the published application). The specification as originally filed does not envision microparticles and compositions that are free of synthetic polymers that cover the broad scope of synthetic polymer. For example paragraph [0042] of the published application describes the lipid-protein-sugar-particles to optionally contain PLGA, PGA, polyesters, polyanhydrides or polyamides and these are not the only synthetic polymers.

Response to Arguments

4. Applicant's arguments filed 03/07/08 have been fully considered but they are not persuasive.

5. Applicant argues that the specification envisions lipid, protein, sugar particles (LPSPs) that do not contain synthetic polymers. But the claims say that it is the composition that does not contain synthetic polymer and not the LPSPs. Furthermore, the specification at page 3, lines 16-18 indicates that, in a preferred embodiment, the LPSPs contain synthetic polymer. The composition, for example in claim 1 comprises (a) and (b) and pharmaceutical carriers.

6. Applicant argues that the as filed specification envisions microparticles are not liposomes and that support for this is provided by the specification at page 23, lines 13 and 14 describing process of preparing the matrix by spray drying … and complex evaporation and that this process does not produce liposomes. This is not found persuasive. For example, Tagawa et al. (US 6,475,517) teaches that liposome is obtained by lyophilization or spray drying (claim 10).

7. Claims 1,7-15,17-20,23-25,27,30,37,47,58-65,80,84,86-91 and 96-107 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. The claims recite derivatives of cellulose and dextran. The boundaries of the derivatives cellulose and dextran are not clear.

9. It is suggested that the term "derivatives" be removed from the claims in order to overcome the rejection.

Specification

10. The disclosure remains objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see paragraph [0011] of the published application, for example). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Please note that applicant did not correct this objection and applicant did not provide any arguments against the request for consideration. However, hyperlinks and/or browser executable code are not permitted in the specification according to MPEP § 608.01.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1, 7, 12-15, 17-20, 23-25, 27, 30, 37, 47, 58-65, 80, 84, 86-91 and 96-99, 101, 103-107remain/are rejected under 35 U.S.C. 103(a) as being unpatentable over Bernstein et al. (US 6,423,345).

Bernstein discloses polymer matrices in the form of microparticles, wherein a lipid, or amphiphilic polymer or other hydrophobic compounds are integrated into polymeric matrix (abstract) and the matrix can be formed of synthetic or natural polymers, including proteins, such as albumin, and polysaccharides (sugars) and vasodilators (column 3, line 31 to column 4, line 22; column 6, line 56 to column 7 line 5).

Bernstein includes therapeutic and prophylactic agents among the active agents, which can be incorporated into the matrix (column 6, line 56 to column 7, line 5). The microparticles of Bernstein can be administered as powder, or formulated in tablets or capsules, or suspended in a solution with pharmaceutically acceptable carriers (column 9, lines 35-47).

The agents described in Bernstein are those that may be labeled with a fluorescent label or an enzymatic or chromatographically detectable agents (column 6, lines 61-63) are diagnostic

agents. With respect to the amounts of lipid, protein and sugar claimed in claims 48-56 of the instant application, Bernstein teaches that the content of the lipid in the matrix is 0.01-60% in relation to the content of the polymer (column 6, lines 18-21) and the amount of polymer (protein) is 0.1-60% (column 4, lines 62-64). Therefore, the patent contemplates an amount of lipid up to 36%. With respect to the size of the claimed size of the microparticles claimed in claims 57-60 and 80 of the application, Bernstein discloses that the microparticles of the invention are manufactured with a diameter suitable for the intended route of administration, and discloses particles for intravascular administration having a diameter of 0.5 to 8 microns (column 2, lines 20-27). With regard to the particle size claimed in instant claim 61, Bernstein is deficient in the sense that the patent fails to disclose particles smaller than 0.5 microns. Applicant has not established comparable example in the specification to demonstrate that the claimed small size provides some unusual and/or unexpected results. It appears to the examiner that the smaller size of particles does nothing additional to the compositions of the invention, especially in view of the teachings of the prior art, that the microparticles of the invention can be administered by any route, including administration to the lungs (column 9, lines 56-63).

With respect to the method of preparing the microparticles claimed in claim 62, Bernstein discloses that the microparticles of the invention can be produced by spray drying the polymer solution formed by dissolving the polymer (protein) and the lipid in the appropriate solvent, dispersing the active agent into the polymer solution (column 8, lines 18-33). With regard to the method of administering an agent claimed in claims 63-65 of the application, Bernstein discloses that the microparticles are combined with a pharmaceutically acceptable carrier and administered to a patient by injection into a blood vessel, subcutaneously,

intramuscularly or orally (column 9, line 64 to column 10 line 6). Oral administration implies placing the microparticles in the oral cavity of the patient, thus the patent contemplates placing the microparticles in a body cavity of the patient, as claimed in claim 65 of the instant application. With respect to the ratio of lipid to protein to sugar claimed in claim 47 and also to the ratios in claims 92 and 95 of the application, it is noted that applicants have no demonstration that the ratio of lipid claimed in the instant application provides unusual/unexpected results and there is no comparable example in the specification to demonstrate that the claimed ratio of lipid provides some unusual and/or unexpected results. It appears to the examiner that the higher ratio of lipid does nothing additional to the compositions of the invention, especially in view of the teachings of the prior art, that the hydrophobic compound integrated in the polymeric matrix modifies the diffusion of water into the microparticle and the diffusion of solubilized drug out of the matrix (column 2, lines 8-11).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to apply the teachings of Bernstein to prepare the microparticles of Bernstein with the expectation for controlled delivery of drugs.

Response to Arguments

14. Applicant's arguments filed 03/07/08 have been fully considered but they are not persuasive.

15. Applicant argues that Bernstein does not teach microparticles comprising lipid, protein and sugar. The examiner had indicated considering applicant's argument when filed. However, upon further consideration of the Bernstein reference, it is clear that there is a disclosure of microparticles (column 1, line 18) and the microparticles comprise hydrophobic compounds such

a DPPC, a lipid (column 2, lines 38-48), natural polymers such as albumin, a protein (column 4, lines 19 and 20) keeping in mind that column 3, lines 35, 36, 37-42 contemplate that synthetic as well as natural polymer can be used to form the matrix. Also, blends of polymers are contemplated and cellulose in column 4, line 21 meets the limitation of the sugar. The limitation for sugar is further met by the teaching that bulking agents include sugars such as mannitol, sucrose, lactose, fructose and trehalose (column 10, lines 8-11 and column 9, lines 64-66 for carriers).

16. Claims 8-11 remain and new claim 102 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bernstein et al. (US 6,423,345) in view of Goldenheim et al. (US 6,534,081).

The teachings of Bernstein et al. have been summarized above. The prior art is deficient in the fact, that it does not specifically include the anesthetics recited in claims 8-10 of the application and anticonvulsant agents, as claimed in claim 11, among the therapeutic agents encapsulated in the microparticles of the invention. Goldenheim provides sustained release dosage forms comprising a local anesthetic and an augmenting agent, and includes bupivacaine, dibucaine, tetracaine and lidocaine among the preferred local anesthetics used in the invention (column 3, line 50 to column 4, line 51). Goldenheim teaches that the local anesthetic is prepared in matrices of controlled release injectable microspheres (column 5, lines 60-64), and the formulations of the invention are suitable for administration in all body spaces and cavities (column 6, lines 55-59). Goldenheim discloses formulations comprising microparticles comprising a local anesthetic, an augmenting agent and a sustained release polymer selected from synthetic polymers, proteins, polysaccharides and combinations thereof (column 7, lines 20-47) and imaging or diagnostic agents (column 7, lines 7, 8, 44-47; column 9, line 40-44) and

the imaging agents meet new claim 102. Thus, the patent provides the general teachings that local anesthetics can be delivered by microparticle compositions and specifically discloses the compounds recited in claims 8-10 of the instant application. With respect to claim 11, Goldenheim includes anticonvulsants among the augmenting agents incorporated in the compositions of the invention (column 12, lines 9-12).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to combine the teachings of Bernstein and the teachings of Goldenheim with the expectation of producing microparticles for the controlled delivery of local anesthetics and anticonvulsant drugs and imaging agents.

Response to Arguments

17. Applicant's arguments filed 03/07/07 have been fully considered but they are not persuasive.

18. Applicant argues that Bernstein does not teach the claimed microparticles and since Goldenheim is relied upon for teaching anesthetic, the rejection should be withdrawn. But it has been described above in response to applicants argument that Bernstein discloses microparticles (column 1, line 18) and the microparticles comprise hydrophobic compounds such a DPPC, a lipid (column 2, lines 38-48), natural polymers such as albumin, a protein (column 4, lines 19 and 20) keeping in mind that column 3, lines 35, 36, 37-42 contemplate that synthetic as well as natural polymer can be used to form the matrix. Also, blends of polymers are contemplated and cellulose in column 4, line 21 meets the limitation of the sugar. The limitation for sugar is further met by the teaching that bulking agents include sugars such as mannitol, sucrose, lactose, fructose and trehalose (column 10, lines 8-11 and column 9, lines 64-66 for carriers).

19. Claims 1 and 100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bernstein et al. (US 6,423,345) in view of Compans et al. (US 4,790,987).

Bernstein is described above as disclosing microparticles (column 1, line 18) and the microparticles comprise hydrophobic compounds such a DPPC, a lipid (column 2, lines 38-48), natural polymers such as albumin, a protein (column 4, lines 19 and 20) keeping in mind that column 3, lines 35, 36, 37-42 contemplate that synthetic as well as natural polymer can be used to form the matrix. Also, blends of polymers are contemplated and cellulose in column 4, line 21 meets the limitation of the sugar. The limitation for sugar is further met by the teaching that bulking agents include sugars such as mannitol, sucrose, lactose, fructose and trehalose (column 10, lines 8-11 and column 9, lines 64-66 for carriers). While Bernstein discloses the delivery of active therapeutic and prophylactic agents among the active agents, which are incorporated into the matrix (column 6, line 56 to column 7, line 5), Bernstein does not teach the delivery of vaccines. However, Compans describes the deliver of vaccine in lipid containing matrix (claims 1-3). Therefore, taking the teachings of the prior art, one having ordinary skill in the art at the time the invention was made would have reasonable expectation of success that incorporating vaccine a matrix composition containing lipid, sugar and protein would provide a matrix composition for effective delivery of vaccines.

20. No claim is allowed.

21. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

22.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BLESSING M. FUBARA whose telephone number is (571)272-0594. The examiner can normally be reached on 7 a.m. to 5:30 p.m. (Monday to Thursday).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/

Supervisory Patent Examiner, Art Unit 1618

/Blessing M. Fubara/
Examiner, Art Unit 1618